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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/927,160	08/09/2001	Sushma Pati	A-64580-4/RFT/RMS/AMS	4009

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EXAMINER	
FALK, ANNE MARIE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 05/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/927,160	PATI ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 January 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-34,36,37 and 41-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-34,36,37 and 41-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed January 24, 2005 (hereinafter referred to as "the response") has been entered. Claims 32, 34, 36, 41, 42, 60, 61, and 65-69 have been amended. Claim 35 has been cancelled.

In the response filed March 9, 2004 Applicants elected without traverse, Group V, Claims 32-37 and 41-70. The elected invention is drawn to a method of making a transgenic mammal comprising a modified endogenous nucleic acid, wherein the preselected target DNA sequence encodes an enzyme. In view of the Election of Species requirement, Applicants further elected a gene encoding a human enzyme.

Claims 32-34, 36, 37 and 41-70 are pending in the instant application.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 32-34, 36, 37, and 41-70 stand rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims cover a method of using a human "female mammal" (recited in Claims 32 and 63) in making a transgenic non-human mammal, which is non-statutory subject matter. Claim 63 further recites producing "at least one mammal" which covers humans despite the recitation in Claim 32 which says that the method is directed to making a transgenic non-human mammal. Inclusion of the phrase "non-human" would be remedial.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32-34, 36, 37 and 41-70 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification fails to provide an enabling disclosure for the claimed method of making a transgenic mammal because the specification does not teach specific phenotypic alterations as a result of the various genetic modifications contemplated. The claimed invention is drawn to methods of making transgenic mammals with no particular phenotype, wherein any endogenous gene encoding an ion-channel protein, a G-protein coupled receptor, an immunoglobulin, a growth factor, an enzyme, or a milk protein, or various other products, is modified in any way. Because the specification discloses no phenotype for the genetically modified mammals, undue experimentation would have been required for one of skill in the art to make and use the claimed invention, as a method of making a product has use only if the product made has use. Given that the phenotype of a transgenic animal or genetically modified animal cannot be predicted and given that only mice with a single point mutation in the gene encoding ornithine carbamoyltransferase have been prepared, one of skill in the art would have been required to exercise undue experimentation to practice the claimed method to make and use any of the other claimed genetically modified mammals.

The specification fails to provide an enabling disclosure for making any type of genetic modification because the only method contemplated for making such genetically modified animals is not enabled for inserting entire genes into specifically selected sites of the target genome. The specification demonstrates that recA-mediated gene targeting can be used to make single base substitutions using recA-coated targeting polynucleotides. However, the specification also discloses that as the region of heterology increases, the stability of four-strand hybrids decreases significantly. Thus, the efficiency of recombination would be expected to be much lower for larger deletions or insertions. While the

specification enables single base substitutions, no guidance is provided for making other types of changes to the genome.

The specification teaches a method of making transgenic mice using a recA-mediated gene targeting strategy. While the specification contemplates the use of the method to make targeted changes to the genome of other mammals, an enabling disclosure is not provided. The specification fails to provide an enabling disclosure for making targeted changes to any mammal other than the mouse because pronuclear microinjection of zygotes typically results in the random integration of the exogenously introduced DNA into the genome of the host and recA-catalyzed gene targeting has not been shown to be as efficient as random integration in any species other than the mouse. Because the efficiency of integration into the genome varies significantly from species to species (see below), one skilled in the art would have been required to exercise undue experimentation in order to practice the claimed method of making the various genetic modifications recited in the claims in any species other than the mouse.

The specification does not contain a written description of genetically modified animals of the type claimed. No particular phenotype is disclosed for the genetically modified animals other than the anticipated expression or inactivation of the modified gene. There is no demonstration that the claimed animals would in fact express the modified genes from the various modified forms contemplated by the claims.

The specification fails to provide an enabling disclosure for the method of making any species of genetically modified mammal harboring alleles of the type claimed because the guidance offered in the specification is not sufficient to teach one of skill in the art how to prepare the claimed genetically modified mammals exhibiting a phenotypic alteration that results from the genetic modification. The mere capability to perform gene transfer in various species is not enabling for the claimed methods because the desired phenotype cannot be predictably achieved by simply introducing any construct into the genome. While gene transfer techniques are well-developed for a number of species, including the

mouse, methods for achieving the desired level of gene expression in appropriate tissues are less well-established. The introduction of DNA into the mammalian genome can ordinarily be achieved most reliably by microinjection or retrovirus-mediated gene transfer. However, the state of the art for transgenics is unpredictable because the method of gene transfer typically relies on random integration of the transgene construct. While the recA-mediated gene targeting method disclosed in the specification relies on site-specific recombination, random integration can also occur and methods for preventing or detecting random integration events are not disclosed. Methods for selecting the desired site-specific recombinant are not disclosed. Therefore, the disclosed method is accompanied by some of the same limitations associated with random integration methods. The resultant genetically modified mammals encompass transgenic mammals generated by random integration of exogenous DNA into the genome. Insertional inactivation of endogenous genes and position effects (see Wall, 1996, p. 61, paragraph 3) can dramatically influence the phenotype of the resultant transgenic animal. Integration of the transgene near highly active genes or, alternatively, in a transcriptionally inactive region, can influence its level of expression. Furthermore, expression of the transgene and the effect of transgene expression on the phenotype of the transgenic animal depends on the particular gene construct used, to an unpredictable extent. The particular genetic elements required for appropriate expression varies from species to species. Thus, a construct that confers the desired phenotype in a mouse cannot necessarily achieve the same result in a rat. Wall (1996) reports that our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior (p. 61, paragraph 3). This is especially relevant for species in which genetic studies are less advanced than in the mouse. Thus, the species-specific requirements for transgene design introduces an additional level of unpredictability associated with the development of transgenic animals. Furthermore, transgene integration efficiency varies from species to species, ranging from 1% in farm animals (cattle, sheep, and pigs) to about 3% in laboratory animals (mice, rabbits, and rats) as reported by Wall (p. 61, paragraph 2). Thus, in the absence of any working examples, the existence of any phenotypic alteration resulting from

the genetic modifications of the type claimed in any species of mammal, is highly unpredictable. Given the lack of working examples and the unpredictability in the art, one of ordinary skill in the art would have been required to engage in undue experimentation in order to practice the claimed methods and use the product produced by the method (i.e., the transgenic mammals).

While the species-specific requirements for transgene design are not clearly understood, examples in the literature demonstrate that even closely related species carrying the same transgene construct can exhibit widely varying phenotypes. For example, several animal models of human diseases have relied on transgenic rats when the development of mouse models was not feasible. Mullins et al., 1990 produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse *Ren-2* renin transgene. Hammer et al., 1990 describe spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human β_2-microglobulin transgenes. Both investigations were preceded by the failure to develop human disease-like symptoms in transgenic mice (Mullins et al., 1989; Taurog et al., 1988) expressing the same transgenes that successfully caused the desired symptoms in transgenic rats.

Given that specific phenotypic alterations cannot be predictably achieved by merely transferring a gene of interest into an animal, specific guidance must be provided to enable the instant invention. The specification must teach those skilled in the art how to practice the full scope of the claimed method and how to use the products produced thereby without undue experimentation. The claims cover methods of making any mammal with any modification in an endogenous gene, but the specification does not enable any modification, other than a single point mutation, in any species, other than the mouse. In the absence of disclosure of genetically modified mammals fully representative of the genetic modifications claimed in the species claimed, and exhibiting an appropriate phenotype, undue experimentation would have been required to practice the claimed invention.

Accordingly, given the demonstrated lack of predictability in the art, the limited amount of guidance given in the specification, the state of the prior art, the quantity of experimentation needed, and

the lack of applicable working examples, one of skill in the art would not be able to practice the claimed invention without undue experimentation.

At pages 9-15 of the response, Applicants argue that the claimed method of making a nonhuman transgenic mammal is broad to any desired phenotype, does not require a "particular phenotype" for enablement, and that the genotypic alteration effected by the claimed method need not change the transgenic animal's phenotype at all. However, the elected invention is drawn to a method of making a transgenic mammal comprising a modified endogenous nucleic acid, wherein the preselected target DNA sequence encodes an enzyme and where the claims recite an insertion sequence, the elected species is a gene encoding a human enzyme. Where the claims are broadly drawn, the claims cover a wide array of specific genetic modifications, resulting from the combination of the numerous preselected target DNA sequences recited in the claims having any type of genetic modification within the target sequence as well as in combination with the numerous insertion sequences also recited in the claims. The specific genetic modifications recited in the claims represent a very large and significant scope within the broad claims. Claims directed to the elected invention, such as Claim 37 which comprises the elected invention where the preselected target DNA sequence encodes an enzyme and Claim 47 which comprises the elected species where the insertion sequence is a-1 antitrypsin, all ultimately depend from the broad, independent Claim 32, thereby demonstrating that the claim covers a very large and significant scope of specific genetic modifications. The claimed methods and the elected invention directed to producing such specific genetic modifications are enabled only if the skilled artisan would know how to use the transgenic animal produced by the method. For the reasons discussed in the prior Office Action and reiterated herein above, the skilled artisan would only know how to use a transgenic mammal that has a useful phenotype. However, for reasons of record, the phenotype of a transgenic mammal is unpredictable and therefore the preparation of a useful (and therefore enabled) transgenic mammal is likewise unpredictable. Applicants' arguments are not commensurate in scope with the scope of the claims nor does it address the scope of the elected invention.

At pages 15-19 of the response, Applicants argue that the method of the present invention may be used to effect large insertions. Applicants further argue that Maga et al. (2003) demonstrates that the use of RecA protein results in significant increase in transgene integration frequencies in livestock production. Thus, Applicants conclude that the claimed methods work and are therefore fully enabled. Contrary to Applicants' arguments, the enablement requirement is not satisfied by addressing only the how to make prong of the enablement requirement because the specification must also teach how to use the claimed invention. A method of making has use only if the product made has a use and one of skill in the art would know how to use the product made. In the instant case, the skilled artisan would not know how to use the wide variety of transgenic mammals covered by the claims, including the elected invention drawn to transgenic mammals having a modified enzyme-encoding gene, for reasons of record. Applicants' arguments are not commensurate in scope with the scope of the claims nor does it address the scope of the elected invention.

At page 19 of the response, Applicants argue that the USPTO has already established as fully enabled Applicants' methods for targeting and altering, by homologous recombination, a pre-selected target DNA sequence in any eukaryotic cell to make a targeted sequence modification. Again, the enablement requirement is not satisfied by addressing only the how to make prong of the enablement requirement because the specification must also teach how to use the claimed invention. The use of a eukaryotic cell is substantially different from the use of a transgenic mammal and the instant specification does not teach how to use the wide variety of transgenic animals covered by the claims, nor the transgenic animals of the elected invention, for reasons of record. Applicants' arguments are not commensurate in scope with the scope of the claims nor does it address the scope of the elected invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32-34, 36, 37 and 41-70 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 32-34, 36, 37 and 41-70 remain indefinite with regard to the "modified endogenous nucleic acid" because it is unclear relative to what standard or point of reference the endogenous nucleic acid is considered to be "modified." Furthermore, it is unclear what would be regarded as an "endogenous nucleic acid." For example, the term could be limited to the genes present in any given individual of the species under consideration, thereby encompassing mutant forms of genes not present in other individuals. At the same time, the gene present in the given individual may have, at one point, been derived from an exogenous source, e.g. a virus. Alternatively, the term could be understood to refer to any form/allele of any gene within the pool of genes of that species, encompassing genes and mutant forms of genes not present in every individual of the species.

At page 20 of the response, Applicants assert that "the terms are standard in the art and would be clearly understood by one skilled in the art because Claim 1 of U.S. Patent No. 6,673,986 recites "a modified genome." However, the claim goes on to recite that "said modification comprises inactivated endogenous immunoglobulin heavy chain loci." Thus, the gene is clearly inactivated, and the modification therefore clearly results in the inactivation of a once active gene. In the instant case, no such point of reference is provided.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing

date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The central official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk
ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER